Original Contribution

A Tale of Two Citizens: A State Attorney General and a Hematologist Facilitate Translation of Research Into US Food and Drug Administration Actions—A SONAR Report

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Abstract

Purpose: Pharmaceutical safety is a public health issue. In 2005, the Connecticut Attorney General (AG) raised concerns over adverse drug reactions in off-label settings, noting that thalidomide was approved to treat a rare illness, but more than 90% of its use was off label. A hematologist had reported thalidomide with doxorubicin or dexamethasone was associated with venous thromboembolism (VTE) rates of 25%. We review US Food and Drug Administration (FDA) and manufacturer responses to a citizen petition filed to address these thalidomide safety issues.

Methods: Case study.

Results: The AG petitioned the FDA requesting thalidomide-related safety actions. Coincidentally, the manufacturer submitted a supplemental New Drug Approval (sNDA), requesting approval to treat multiple myeloma with thalidomide-dexamethasone. FDA safety officers reviewed the petition and the literature and noted that VTE risks with thalidomide were not appropriately addressed in the existing package insert. In the sNDA application, the manufacturer reported thalidomide-associated toxicities for multiple myeloma were primarily somnolence and neurotoxicity, and a proposed package insert did not focus on VTE risks. In October, the FDA informed the Oncology Drug Division that VTE risks with thalidomide were poorly addressed in the existing label. After reviewing this memorandum, an Oncology Drug Division reviewer informed the manufacturer that approval of the sNDA would be delayed until several thalidomide-associated VTE safety actions, including revisions of the package insert, were implemented. The manufacturer and FDA agreed on these actions, and the sNDA was approved.

Conclusion: New approaches addressing off-label safety are needed. The conditions that facilitated the successful response to this citizen petition are uncommon.

Introduction

Drug toxicities that occur in off-label clinical settings raise public health concerns. We review the efforts of a state attorney general (AG) to require that the US Food and Drug Administration (FDA) address this concern. We also report on the 6-year follow-up of safety-related commitments negotiated between the FDA and manufacturer in the course of addressing these concerns.

In 2004, then Connecticut AG Richard Blumenthal initiated investigations into thalidomide, concerned that 92% of its prescriptions were for off-label use.[1] In 2005, after identifying safety concerns in this setting, the AG, in collaboration with a hematologist (C.L.B.), filed a citizen petition requesting that the FDA take action to inform the medical community of venous thromboembolism (VTE) risks in off-label settings.[2] This was the fourth citizen petition filed with the FDA by a state AG, and the second petition filed with the FDA by the Connecticut AG (Appendix Table A1, online only). Previous petitions had been rejected by the FDA. Herein, we report on FDA responses to this petition.

A citizen petition is a process afforded under Section 10.30 of Title 21, Volume 1, of the Code of Federal Regulations. It permits any person to request the FDA Commissioner to "issue, amend, revoke a regulation or order or take or refrain from taking any other form of administration action" over which the commissioner has statutory authority.

The subject of this petition—thalidomide—is among the most storied of all pharmaceuticals. Intended as a substitute for barbiturate-based sleeping medications, thalidomide was available as an over-the-counter drug in West Germany in the 1950s and 1960s.[3,4] In 1960, the Merrell Company submitted a New Drug Application (NDA) for thalidomide to the FDA as a sedative.[5] This application was denied when FDA medical officer Frances Kelsey identified neurotoxicity concerns.[5] By 1961, birth defects had been linked to thalidomide-treated pregnant women, and the drug was withdrawn from worldwide use.[6] Unexpectedly, in 1965, the therapeutic potential of thalidomide in treating erythema nodusom leprosum (ENL) was discovered when patients with leprosy, prescribed the drug for its sedative properties, experienced improvement of their lesions.[7] The FDA granted marketing approval for thalidomide for cutaneous manifestations of ENL in 1998 based on historical data.[7-9] In 1997, cancer trials evaluating thalidomide had begun based on unexpected benefit identified in patients with

multiple myeloma at University of Arkansas.[10,11] In 2000, a 32% response rate among patients with refractory multiple myeloma was reported.[10] Thus began the rebirth of thalidomide.

Methods

Data include the petition and FDA correspondence (2003 to 2011).[12-19] We reviewed correspondence between the Connecticut AG and FDA as well as internal FDA communications.

Results

Results are summarized in Table 1.

2000 to 2002: VTEs

Two phase II trials of thalidomide and concomitant chemotherapy for patients with cancer were terminated when VTE rates > 25% were identified.[19,33] University of Arkansas clinicians reported high VTE risks when patients with multiple myeloma received thalidomide-doxorubicin.[20] A review conducted by a hematologist director of the Southern Network on Adverse Reactions (SONAR) program identified a 16% VTE rate in multiple myeloma trials of thalidomide with chemotherapy or dexamethasone.[34] The FDA had received only 67 reports of VTE among 29,464 patients enrolled in the thalidomide safety program, the System for Thalidomide Education of Providers on Safety (STEPS).[22,34]

2003: Initial Actions

Thalidomide received regulatory approval in Australia, Europe, and Asia as single-agent treatment for multiple myeloma. Labels warned of VTE risks, particularly with erythropoietin coadministration, and recommended VTE prophylaxis[35] (Table 2). After the FDA Office of Drug Safety became aware of 170 thalidomide-associated VTEs, the FDA requested revised product labels indicating that off-label treatment of cancer with thalidomide had VTE risks, and it was unknown if concomitant therapies were contributory; the sponsor agreed.[15] Concurrently, the sponsor submitted a supplemental NDA (sNDA) for FDA approval of single-agent thalidomide for refractory multiple myeloma.[36]

2004: Additional Concerns

The acting director of the FDA Division of Oncology Drug Products informed the sponsor that the sNDA was nonapprovable, because bortezomib had recently received FDA approval in that setting. The FDA noted that an sNDA for thalidomide-dexamethasone for newly diagnosed multiple myeloma based on results from a phase III trial by the Eastern Cooperative Oncology Group was preferred.[12]

The AG initiated an investigation of off-label marketing of thalidomide amid reports that the sponsor had imposed several price increases, despite 92% of thalidomide usage being off-label, and noted that the Medicare Replacement Drug Demonstration Project included the drug as a reimbursable off-label treatment for multiple myeloma.[1,37,38]

At the American Society of Hematology conference, C.L.B. updated his review of VTE risks. Among 1,784 patients in clinical trials, a VTE rate of 15% was noted for patients with multiple myeloma receiving thalidomide with chemotherapy or dexamethasone, with VTE rates as high as 43% with thalidomide plus chemotherapy treatment in other cancers.[2] The FDA received 190 VTE reports among 101,164 thalidomide-treated patients.[2]

2005: The Petition

The AG's office reviewed a press release summarizing the presentation by C.L.B.[39] The AG concluded that thalidomide labeling did not provide sufficient safety information on off-label thalidomide for patients with cancer also receiving dexamethasone, doxorubicin, or erythropoietin. A Connecticut Assistant AG and C.L.B. discussed options to disseminate these concerns.[40] In 2004, the AG filed his first petition, outlining safety concerns with oxycontin.[41] The AG concluded that similar action was needed for thalidomide, and he filed a petition.[23] This was part of a strategy to use his office to raise awareness of safety concerns when pharmaceuticals were primarily administered in off-label settings. The petition indicated that the international partner of the sponsor had disseminated VTE warnings with thalidomide, including encouraging VTE prophylaxis (Table 2).[35] The petition included a report from C.L.B. identifying a 16% VTE rate in trials of patients with cancer receiving thalidomide with dexamethasone or doxorubicin. However, the FDA had received reports of only 283 thalidomide-associated VTE events among 140,000 thalidomide-treated patients with cancer.[42] The AG requested that the FDA require black-box warnings, a phase III clinical trial to evaluate thromboprophylaxis, a "dear doctor" letter, and STEPS expansion to include VTE information. The petition included comparisons of US product label warnings with Australian product label warnings and summarized sponsor statements to investors highlighting neuropathy and sedation as the most common serious toxicities. Independently, the sponsor submitted to the FDA an sNDA for thalidomide-dexamethasone for multiple myeloma. The FDA designated this sNDA for priority review, with a 6-month review period.[43]

Reviewers at the FDA Office of Drug Safety reported to the Oncology Drug Division that thalidomide as a cancer treatment had VTE safety concerns not appropriately addressed in the existing label.[12] FDA reviewers identified 19 multiple myeloma clinical trials with VTE rates up to 28% with thalidomide plus dexamethasone or chemotherapy, and recommended that the Division of Oncology Drug Products request that the sponsor revise existing black-box warnings and disseminate dear doctor letters describing these concerns.[12]

Two weeks before the sNDA review deadline, and in response to the VTE report from the Office of Drug Safety, the acting director of the Division of Drug Oncology Products informed the sponsor that approval of the sNDA would be delayed until the manufacturer initiated several safety actions related to VTE risks.[12]

Table 1. Timeline for Thalidomide-Associated VTE Safety Evaluations

		VTE Reports in FDA Databases*		VTE Reports in Clinical Trials With Chemotherapy or Corticosteroids	
Year	**Comment or Event**	**No.**	**VTE Rate (%)**	**No.**	**VTE Rate (%)**
2002	Zangari et al[20] report high rates of thalidomide-associated VTEs in cancer setting	67 of 29,464	0.2	108 of 827	16
2003	FDA ODAC reviews failure of sponsors to complete postapproval commitment studies (clinical trials)[21]				
2003	Thalidomide receives regulatory approval in Australia, New Zealand, Turkey, and Israel as single-agent treatment for multiple myeloma; package inserts disseminated by international partner of US sponsor warn of VTE risks with concomitant administration of other drugs and that prophylaxis should be considered[22]				
2003	FDA Office of Drug Safety becomes aware of increasing numbers of thalidomide-associated VTEs[2]	170 of 73,435	0.2		
2003	US sponsor requests FDA approval of thalidomide as single-agent therapy for multiple myeloma[2]				
2003	FDA requests and sponsor agrees to revision of package insert warning regarding thalidomide for cutaneous manifestations of ENL treatment, indicating that off-label treatment of cancer or inflammatory conditions "may have increased VTE risk, and it is not known if concomitant therapy with other medications is contributory"[14]				
2004	C.L.B. reports at American Society of Hematology conference on high rates of thalidomide-associated VTEs[1]	190 of 101,164	0.2	223 of 1,784	15
2004	Connecticut AG Blumenthal initiates investigation of thalidomide				
2004	FDA informs sponsor that application for approval of thalidomide as single-agent therapy for multiple myeloma was nonapprovable[2]				
May 2005	Connecticut AG files citizen petition outlining VTE risks with off-label thalidomide[1,23]	283 of > 140,000	0.2	585 of 4,863	16
May 2005	US sponsor requests FDA approval of thalidomide as treatment for multiple myeloma[2]				
May 2005	Connecticut AG holds press conference indicating that he filed citizen petition about thalidomide safety risks[23]				
May 2005	FDA informs sponsor that application for accelerated approval of thalidomide-dexamethasone for multiple myeloma has been granted priority review status, with decision by November 2005[2]				
June 2005	Congressman Ed Markey releases report identifying low rates of completion of postapproval commitment studies by sponsors who receive accelerated approval for cancer indications[24]				
September 2005	US sponsor informs FDA Office of Oncology Drugs that no new safety concerns had arisen during recently completed licensing trial evaluating thalidomide administration to those with multiple myeloma; sponsor indicates that trial identified neuropathy and somnolence as most important serious toxicities[2]				
October 2005	FDA reviewers with Office of Drug Safety report to acting director of FDA Division of Oncology Drug Products that after reviewing petition and additional data, VTE risks are significant with thalidomide administration to those with multiple myeloma, and several recommendations outlined in petition should be considered[2]				
November 2005	Acting director of FDA Division of Oncology Drug Products informs sponsor that VTE risks with thalidomide as multiple myeloma treatment need to be addressed in proposed product label before FDA approval is granted[2]				
December 2005	As part of FDA approval for lenalidomide for myelodysplasia, sponsor includes black-box warning of VTE risks with off-label lenalidomide administration to those with multiple myeloma patients[16]				
February 2006	FDA reviewer for Division of Oncology Drug Products informs sponsor that review of licensing trial has identified questions about VTE prophylaxis failure and VTE treatment[2]				
May 23, 2006	Sponsor submits proposed VTE safety language to FDA that does not include information on potential benefit of prophylaxis; FDA informs sponsor that this language is not acceptable[2]				

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Table 1. (continued)

Year	Comment or Event	VTE Reports in FDA Databases*		VTE Reports in Clinical Trials With Chemotherapy or Corticosteroids	
		No.	VTE Rate (%)	No.	VTE Rate (%)
May 24, 2006	Sponsor submits revised VTE safety language including information on prophylaxis; director of Division of Oncology Drug Products informs sponsor that accelerated approval of thalidomide with dexamethasone for multiple myeloma is now approved[2]				
May 24, 2006	Sponsor commits to conducting postapproval epidemiologic study of VTE prophylaxis and treatment among patients with multiple myeloma who receive thalidomide[2,13]				
May 24, 2006	Director of Division of Oncology Drug Products informs Connecticut AG that four of six safety requests in citizen petition have been granted, and sponsor had incorporated them into product label[25]				
December 2006	Bennett et al[23] report in *JAMA* high rates of VTE with thalidomide and lenalidomide treatment of cancer patients[26]	1,118 of >200,000	0.5	930 of 3,082	18
2008	Confirmatory phase III trial reports 23% VTE rate with thalidomide-dexamethasone[27]				
2008	34 hematologists recommend individualized risk approaches with thalidomide for multiple myeloma, with consideration of viscosity and concomitant high-dose dexamethasone or chemotherapy administration[28]				
2009	GAO report indicates that many cancer drugs granted accelerated approval do not have completed confirmatory clinical trials[29]				
2009	FDA responds to ODAC report indicating that delays in postapproval commitment studies are primarily because of difficulty recruiting patients to clinical trials[30]				
2010	ODAC identifies continuing problems with completion of post–accelerated approval commitments; FDA pledges to hold annual ODAC review of status of these commitments[31]				
2011	Sponsor and FDA continue to negotiate details over study protocols for epidemiologic assessments of VTE risks and treatment among thalidomide-treated patients with multiple myeloma[13]				
2011	ODAC recommends that FDA improve its enforcement actions related to post–accelerated approval commitments, focusing on clinical trials[32]				

Abbreviations: AG, attorney general; ENL, erythema nodusom leprosum; FDA, US Food and Drug Administration; GAO, Government Accountability Office; *JAMA*, *Journal of the American Medical Association*; ODAC, Oncology Drug Advisory Committee; STEPS, System for Thalidomide Education of Providers on Safety; VTE, venous thromboembolism.

* Denominator data were based on number of thalidomide-treated patients with cancer included in the STEPS registry at each of the various time points.[9]

January to May 2006: FDA Responds to the Citizen Petition

In February, the FDA reviewer in the Oncology Drug Division informed the sponsor that review of the proposed licensing trial results had identified questions about VTE prophylaxis failure among thalidomide-treated patients with multiple myeloma.[12]

In May, an officer with the FDA Division of Drug Marketing, Advertising, and Communications informed the sponsor that thalidomide-associated VTE claims included in the proposed package insert were misleading, minimized VTE risks, and failed to communicate preliminary data suggesting benefit from concurrent prophylactic therapy or aspirin. The division recommended that the sponsor report this information in a black-box warning.[12]

The next day, the sponsor submitted revised language to the FDA in response to these recommendations. The Director of the Center for Drug Evaluation and Research indicated that this revision was acceptable, and the sNDA was approved. The director then informed the AG that the FDA had granted, and the sponsor had agreed to, all but two requests in the petition[25] (Table 3). The granted requests included stronger VTE warnings, advising consideration of prophylaxis, and dissemination of "dear health care professional" letters.[16] The request for a phase IV trial evaluating VTE prophylaxis was denied, because the Oncology Drug Advisory Committee raised feasibility concerns. The request to expand STEPS to include VTE information was also denied; the FDA expressed concern that it could compromise teratogenicity prevention. The FDA requested that the sponsor develop a protocol and study VTE treatment and prophylaxis among thalidomide-treated patients enrolled in STEPS; the sponsor agreed.

June 2006 and Beyond: Subsequent Developments

In December, a report in *Journal of the American Medical Association* by C.L.B. indicated that the FDA had received 1,118 thalidomide-associated VTE reports.[26] Thirty-five trials identified a VTE rate of 18% with thalidomide-dexamethasone,

Table 2. Summary of Requested Revisions Outlined in Connecticut AG's Citizen Petitions and FDA Responses

Category	Request*	Response†
Black-box warning	Strengthen warning concerning heightened risk of VTE in black-box warning	Agreed with request and requested that sponsor add information on VTE prophylaxis
Warnings	In Warnings section, add additional bolded warnings on thrombotic events, adverse reactions, and other adverse events in published literature or reported from older sources; add new section "Other adverse events observed in cancer patients" to Adverse Reactions section	Agreed with this request, but required changes in sections of label that differed from those included in petition; Warnings section was revised to include information about VTE risks and potential prophylaxis; "Adverse events in multiple myeloma controlled trials" section was added to Adverse Reactions section, with information on thrombosis/embolism added
Phase IV clinical trial	Conduct trial to determine most effective regimen for thalidomide-related VTE prophylaxis	Denied this request based on discussions with Oncologic Drug Advisory Committee members over previous 12 months
"Dear doctor" letter	Notify prescribers of increased potential for VTEs with thalidomide and other cancer therapies	Agreed with this request, and requested that sponsor issue this letter
Risk-management program (STEPS)	Expand to provide VTE education and obtain VTE clinical information for all patients in effort to reduce risk of incidence of thrombotic events	Modified this request; FDA requested that sponsor conduct prospective epidemiologic study of VTE prophylaxis, initial VTEs, recurrent VTEs, and VTE treatment for selected patients in STEPS program
	All other actions necessary to protect the integrity of the STEPS program	No specific action was requested by AG

Abbreviations: AG, attorney general; FDA, US Food and Drug Administration; *JAMA*, *Journal of the American Medical Association*; sNDA, supplemental New Drug Approval; STEPS, System for Thalidomide Education of Providers on Safety; VTE, venous thromboembolism.

* Citizen petition was filed on May 4, 2005. Supporting safety information appeared in *JAMA* on December 6, 2006.

† FDA responsed to the requests on May 25, 2006. The sponsor revised the package label on May 26, 2006 (the same day that the sNDA for multiple myeloma was approved).

thalidomide-doxorubicin, or thalidomide and chemotherapy treatment for several cancers.[26]

In 2008, a phase III trial involving patients with newly diagnosed multiple myeloma reported a VTE rate of 23% with thalidomide-dexamethasone. VTE prophylaxis was rarely administered during the trial.[26] This publication described results of the licensing trial for the sNDA for multiple myeloma.

In 2012, the sponsor has continued to negotiate study protocol details with the FDA for evaluating VTE prophylaxis and treatment among thalidomide-treated patients with multiple myeloma (a postapproval commitment agreed to in 2006).[14]

Discussion

The citizen petition was instrumental in facilitating FDA safety actions, which probably would not have occurred until several years later had it not been filed. In 2003, the FDA requested that the product label be revised to inform physicians that thrombotic events had been reported in patients treated with thalidomide, that patients with inflammatory diseases or cancer have an increased incidence of VTEs, and that it is not known if concomitant therapy with other medications had been contributory. In 2005, the sponsor informed the FDA that safety concerns for thalidomide treatment of multiple myeloma were similar to those for ENL: somnolence and neurotoxicity (failing to highlight VTE).[12] As noted by reviewers at the FDA Office of Drug Safety in FDA communications in 2005, the impetus for review of thalidomide-associated VTEs was the report from C.L.B. identifying cancer trials with high VTE rates with thalidomide and concomitant dexamethasone or chemotherapy.[44] Among patients with multiple myeloma, VTE rates were as high as 33% when thalidomide and concomitant chemotherapy were administered. In this communication, FDA reviewers from the Office of Drug Safety reported that they had reviewed thalidomide-associated VTEs in the setting of multiple myeloma. This review identified VTE rates of 3% to 5% with thalidomide, 8% with thalidomide and dexamethasone, and 8% to 28% with thalidomide and concomitant chemotherapy. The reviewers indicated that they agreed with C.L.B.'s report on high VTE rates with thalidomide with corticosteroids or doxorubicin, and communicated this safety concern to the acting director of the Division of Oncology Drug Products. One month later, the acting director communicated this concern to the manufacturer and informed the manufacturer that this new finding necessitated a delay in the sNDA approval of thalidommide. This was the first mention of VTE risks in communications from the Division of Oncology Drug Products to the manufacturer.[12] This experience highlights a deficiency in the FDA safety review process—a majority of safety concerns that reviewers of NDAs and sNDAs evaluate are identified by sponsors.[25-27]

On May 25, 2006, the FDA recommended, and the sponsor agreed to, a revised black-box label, dear doctor letter, and medication guide describing VTE risks with thalidomide-dexamethasone treatment of myeloma.[25] The AG received a letter from the acting director of the Division of Oncology Drug Products indicating that the FDA had reviewed the requests from the AG.

The observation that dissemination of VTE risk notification occurred after the filing and resolution of the petition suggests that the petition was instrumental in bringing about FDA safety actions. The VTE rate of 23% with thalidomide-dexamethasone treatment of multiple myeloma and low rates of VTE prophylaxis among patients in the phase III licensing study were described in a 2008 publication.[26] This information had been included previously in the revised product label issued by the manufacturer in May 2006. The first mention of this

Table 3. Product Labels for Thalidomide From Australia (2003), From the United States (2003 and 2006), and As Proposed by Connecticut AG Richard Blumenthal (2005); Product Label for Lenalidomide in the United States (2005); and Dear Health Care Professional Letter From Europe on Lenalidomide-Associated Arterial and VTE (2011)

Label/Letter	Details
Product label for thalidomide as treatment for refractory multiple myeloma in Australia (October 2003; Warning section)	
DVT and PE	An increased risk of DVT and PE has been reported in patients treated with thalidomide. The risk appears to be greatest during the first 5 months of therapy. Previous history of thromboembolic events or concomitant administration of erythropoietic agents or other agents such as hormone replacement therapy, may increase thrombotic risk. Therefore, these agents should be used with caution in multiple myeloma patients receiving thalidomide with prednisone and melphalan. Particularly, a hemoglobin concentration above 12 g/dL should lead to discontinuation of erythropoietic agents. Patients and physicians are advised to be observant for signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis should be administered for at least the first 5 months of treatment, especially in patients with additional thrombotic risk factors. Prophylactic antithrombotic products, such as low molecular weight heparins or warfarin, should be recommended. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors. If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilized on anticoagulation treatment and complications of thromboembolic events have been managed, thalidomide may be restarted at the original dose dependent upon a benefit-risk assessment. The patient should continue anticoagulation therapy during the course of thalidomide treatment.
Product label for thalidomide as a treatment for cutaneous manifestations of ENL, after reports of thalidomide-associated VTE were received by the FDA (October 2003; Warning section)	
Thrombotic events	Thrombotic events have been reported in patients treated with thalidomide. Patients with neoplastic and various inflammatory conditions being treated with thalidomide may have an increased incidence of PE, deep vein thrombophlebitis, thrombophlebitis, or thrombosis. It is not known if concomitant therapy with other medications, including anticancer agents, is a contributing factor.
Connecticut AG Richard Blumenthal's proposed product label for thalidomide as treatment for cutaneous manifestations of ENL (May 5, 2005; black-box warning)	
VTEs	In malignant conditions, such as multiple myeloma, patients are predisposed to a hypercoagulable state. Thus, caution should be used when thalidomide is combined with chemotherapy, as VTE is a potential complication. An unexpectedly high risk of VTE has been observed when thalidomide is combined with chemotherapy for newly diagnosed patients with myeloma. The potential for experiencing thrombotic events is particularly acute when thalidomide is used concomitant with vincrisine, doxorubicin, and dexamethasone.
Product label for thalidomide after FDA approval as treatment for newly diagnosed multiple myeloma (May 25, 2006; black-box warning)	
VTEs	The use of thalidomide in multiple myeloma results in an increased risk of VTEs, such as DVT and PE. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of VTE events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared with 4.9% in patients receiving dexamethasone alone ($P = .002$). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment.

Abbreviations: AG, attorney general; DVT, deep vein thrombosis; ENL, erythema nodusom leprosum; FDA, US Food and Drug Administration; PE, pulmonary embolus; VTE, venous thromboembolism.

high VTE rate observed the clinical trial in communications by the FDA Division of Oncology Drug Products occurred in February 2006, 2 months after the original decision date for action on the sNDA. Had the sNDA been approved in 2005, as seemed likely, absent VTE concerns raised by the petition, it is doubtful that the manufacturer would have included this information in the product label at that time.

VTE concerns remain. In 2008, hematologists recommended individualized-risk approaches with thalidomide, with consideration of viscosity and concomitant high-dose dexamethasone or chemotherapy administration.[28] Guidelines identify VTE risks when patients with multiple myeloma receive thalidomide with dexamethasone, doxorubicin, or erythropoietin.[43,45] Whereas the petition identified thalidomide-associated VTE risks for several cancers, the FDA commented only on multiple myeloma, despite thalidomide use for many cancers. VTE prophylaxis trials continue to be requested by clinicians.[43] In 2012, the manufacturer has yet to successfully negotiate with the FDA a study protocol of VTEs among patients with thalidomide-treatment multiple myeloma.

Multiple factors contributed to the success of the petition. Approximatley 200 citizen petitions are filed annually.[46] Pharmaceutical manufacturers often petition for delays in approval of competitor products. The Public Citizen organization frequently petitions for stronger warnings or withdrawal of FDA approval for drugs with serious toxicities. Advocacy groups often petition for access to novel therapeutics and expanded FDA approval. Overall, the FDA denies 70% of these petitions.[46]

It should be noted that this petition was drafted over months. Several versions were revised by C.L.B. and assistant AGs. This effort was time consuming and conducted because of a strong concern from the AG that thalidomide was being prescribed almost exclusively off label as a cancer drug to thousands of individuals. From the AG's perspective, the petition placed policy concerns squarely before relevant agencies; it was a measured approach for raising investigative findings and seeking solutions, and it offered an alternative to litigation.

This study highlights issues related to the use of the citizen petition to address safety concerns. Petitions can be perceived as intrusive in the internal workings of an administrative agency. However, familiarity with the law, a solid scientific basis for petitioning the FDA, the degree of relation between the requested actions and safety concerns raised, and timing of a petition contributed to a petition being viewed more positively. The saliency of the subject drug with its storied past may also have affected the processing of this petition. Furthermore, the amount of new information that the petition brought to the attention of the FDA may have positively affected its success. Another consideration was that it addressed safety concerns involved in off-label use.

The successful petition for thalidomide benefited from a unique confluence of factors—the most important of which was perhaps the timing of the petition, coinciding with the premarket thalidomide sNDA. The approval of the sNDA was particularly important to the manufacturer, because thalidomide was the primary drug marketed by the manufacturer; the only FDA approval for thalidomide at that time was for erythema nodosum leprosum, and the previous sNDA application for thalidomide treatment of multiple myeloma had been rejected. With the revised sNDA under review, FDA officials may well have understood that the sponsor had a great incentive to comply with requests for labeling changes. The petition was filed at a time when the FDA was able to leverage its strong preapproval power to command certain postapproval labeling changes (in area in which FDA authority is generally weaker).

The response to the petition highlights the dichotomy between *ex ante* (preapproval) and *ex post* (postmarketing) FDA powers.[3,4,47] Before approval of a new drug, the FDA is the sole arbiter of the marketability of a drug. Without FDA approval, a new drug cannot be prescribed or sold. Once approval is granted, the postmarketing powers of the FDA are limited.

Our experience shows that the passage of the Prescription Drug User Fee Act in 1992, which permitted expedited drug approval, may have exacerbated the inability of the FDA to hold manufacturers accountable for postapproval safety actions. Congressman Ed Markey of Massachusetts and the Government Accountability Office reported that the FDA had not required sponsors to complete several agreed-on postaccelerated approval commitment studies.[19,26] The FDA rejected these conclusions, emphasizing accrual barriers to phase IV postapproval trials.[29] We identified a different concern—the FDA and sponsor have yet to agree on even the protocol design for a postaccelerated approval epidemiologic study of thalidomide, 6 years after the commitment was negotiated. Since 2007, the FDA has the authority to impose civil penalties for failure to complete postapproval commitment studies.[48] Financial penalties could induce the sponsor to conduct this study.

Future research should identify factors associated with successful petitions and how these factors relate to the internal workings of the FDA. These analyses should explore whether factors that conform to the procedural legitimacy of the FDA, or factors that recognize the powerful influence of attorneys within the agency, are more likely to receive a positive outcome. The nonprofit organization Public Citizen has the most experience with successful petitions. It would be of broad interest to learn of the factors that characterize successful Citizen Petitions; however, it should be noted that the organization has a litigation group that facilitates comprehensive filings of FDA petitions.

We conclude that the petition facilitated translation of research findings into practice. However, delays in initiating mandated postapproval studies for thalidomide have occurred, similar to those reported for postapproval commitments involving clinical trials.[21,24] Additional safety actions for VTEs associated with thalidomide, beyond the filing of citizen petitions, are needed. We also emphasize the observation that safety reviews do not end with revision of a product label and dear doctor letter. The manufacturer and FDA have yet to negotiate the details of an agreed-on epidemiologic study of thalidomide-associated VTEs, and the clinical uncertainty of VTE prophylaxis with thalidomide persists. Attention must be paid to pharmaceutical safety over the entire lifetime of a drug, particularly one with as storied a history as thalidomide.

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Author Contributions

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Appendix

Table A1. Citizen Petitions Filed With FDA by State AGs (2002 to 2005)

Year	AG	Request	FDA Response
2002	40 state AGs	FDA should regulate smokeless tobacco product as food or drug*	Denied (2003)
2004	Illinois AG and Illinois Governor	FDA should allow Illinois residents to purchase pharmaceuticals from Canada†	Denied (2004)
2004	Connecticut AG	FDA should add black-box warnings, require "dear doctor" letter, and disseminate public health advisory indicating that dosing of oxycodone every 8 hours was unsafe‡	No response received; in 2008, Connecticut AG sued FDA requesting response; this suit was also unsuccessful
2005	Connecticut AG	FDA should take six steps to improve safety of thalidomide§	Four of six requests were granted (2006)

Abbreviations: AG, attorney general; FDA, US Food and Drug Administration.
* National Comprehensive Cancer Network: http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf
† Palumbo A, Rajkumar SV, Dimopoulos MA, et al: Leukemia 22:414-423, 2008.
‡ Evens AE, Tallman MS, Singhal S, et al: http://www.fda.gov/ohrms/dockets/dockets/05p0167/05p-0167-cp00001-Tab-03-RADAR-DRAFT-vol1.pdf
§ State of Connecticut: http://www.ct.gov/ag/lib/ag/press_releases/2005/health/celgene_petition.pdf